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HERITABLE DISORDERS OF CONNECTIVE TISSUE

III. The Marfan Syndrome

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HISTORICAL SURVEY

IN 1896[101] the gross skeletal manifestations of the syndrome which bears his name were described by Marfan,* who called the condition *dolichostenomelia* (long, thin extremities). The condition was renamed arachnodactyly by Achard in 1902.[3] Salle[136] in 1912 reported necropsy observations in the case of a 2½-month-old infant who died with cardiac symptoms and showed generalized dilatation of the heart and patent foramen ovale. Boerger[24] first clearly related ectopia lentis to the other manifestations. As is usually the case, vague references to cases of what was certainly this syndrome can be found in medical reports antedating the definitive descriptions. For instance, Williams,[183] an opthalmologist in Cincinnati, in 1876 described ectopia lentis in a brother and sister who were exceptionally tall and had been loose-jointed from birth.

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*Antoine Bernard-Jean Marfan (1858-1942), Parisian professor of pediatrics, did much to establish pediatrics as a specialty in France and elsewhere. He was the author of several widely read textbooks and monographs on pediatric topics and editor of *Le Nourrison* for a great many years. In addition to the syndrome under discussion here, his name is often attached to Marfan's law (that immunity to pulmonary phthisis is conferred by the healing of a local tuberculous lesion) and Marfan's subxiphoid method for aspirating fluid from the pericardial sac. (For other biographic details, see references 6, 7, 8, 74; for portrait, see reference 8.)

Weve of Utrecht,[177] publishing in 1931, first clearly demonstrated the heritable nature of the syndrome and its transmission as a dominant trait. Furthermore he conceived of this syndrome as a disorder of mesenchymal tissues and accordingly designated it *dystrophia mesodermalis congenita, typus Marfanis.*

The major cardiovascular complications, namely, aortic dilatation and dissecting aneurysm, were first clearly described in 1943 by Baer, Taussig, and Oppenheimer[11] and by Etter and Glover,[42] respectively. Again, although earlier reports of the aortic complications can be discovered (e.g., reference 29), these latter authors first drew attention to them and opened the way for clearer recognition of the internal medical implications of this syndrome in adults.

"Marfan's syndrome," or better, "the Marfan syndrome," is, in my opinion, the preferred designation until such time as the basic defect is known and an accurate name based thereon can be devised. Arachnodactyly is, on the one hand, not striking in some patients, and, on the other hand, occurs with other developmental disorders, both acquired and genetic.

Probably at least 350 cases of the Marfan syndrome have been reported in the literature. By intensive searches of multiple sources, I was able in the last three years to collect 50 kinships in which at least one bona fide affected person has occurred. Nineteen of these definitely affected families are represented in the accompanying illustrative material and data from seven other definitely affected families have been presented elsewhere.[92] The total number of affected persons in these pedigrees is in excess of 100. In this study, the Wilmer Ophthalmological Institute of The Johns Hopkins Hospital was the largest single source of propositi. However, other sources included pediatricians, orthopedists, endocrinologists, and cardiologists. The Medical Examiner's Office was another fruitful source; tracing the relatives of young individuals dying of dissecting aneurysm of the aorta revealed several affected kinships.

CLINICAL MANIFESTATIONS

Elsewhere[92] is presented a "pedigree of causes" in which the several manifestations of the Marfan syndrome are related to the hypothesized, but, as yet, undefined fundamental defect of connective tissue.

The Skeletal Aspects (see Fig. 1 for the various body types encountered).—Dolichomorphism characterizes the skeletal abnormality of the syndrome. The victim often suggests the subject of an El Greco painting.* The extremities are long, and characteristically the lower segment (pubis-to-sole) measurement is in excess of the upper segment (pubis-to-vertex) measurement and the arm span in excess of the height. In general, the more distal bones of the extremities tend to demonstrate this excess length most strikingly. Arachnodactyly is the result (Fig. 3). At times the great toes are elongated out of proportion to the others (Fig. 3,*B*).[47,163] The ribs participate in the excessive longitudinal growth with formation of pectus excavatum (Fig. 1,*C*), "pigeon breast" (Fig. 1,*B*) or less symmetrical varieties (Fig. 4,*A*) of thoracic cage deformity. The bones of the skull and face are likewise affected with resulting dolichocephaly, highly-arched

*Astigmatism is thought to have been the basis for El Greco's distorted representations, as in "St. Martin and the Beggar" (National Gallery, Washington, D. C.)

palate, long, narrow face, and prognathism. There may be "spurring" of the heels as a result of excessive length of the os calcis.

Skeletal proportions are more important than actual height. It is true that these patients are often very tall. One patient was 6 feet tall at the age of 12 years.[30] Another patient[180] was 7 feet tall. The tallest patient encountered in our investigations was 6 feet 7 inches tall.

Redundancy and "weakness" of joint capsules, ligaments, tendons, and fascia is responsible for a large group of manifestations which include pes planus, genu recurvatum, hyperextensibility of joints, habitual dislocation of hips,[63] patella,[110] clavicles, mandible, and other joints, ganglia,* hernias, synovial diverticula,* kyphoscoliosis. The "flat feet" are often so advanced that the internal malleolus literally rest on the floor (Fig. 3,*D*). Kyphoscoliosis can be very severe (Fig. 4,*B*). In rare instances, hemivertebra is responsible in part for spinal deformity.[90] At times, the spinal deformity has been thought to be due to Scheuermann's epiphysitis.[99] Even femoral hernias occur rather commonly in men with Marfan's syndrome, and diaphragmatic hernia has been present in some of our patients. Hydrocele is occasionally present.

Muscular underdevelopment and hypotonia is a frequent[46,160] but by no means invariable feature. This feature has been so striking as to suggest a primary disorder of muscle in some instances. (The converse error of diagnosis—primary muscular dystrophy called Marfan's syndrome—has occurred in isolated instances.) It is probable that the muscular manifestations are secondary to the abnormality of bones and joints and to abnormality of the perimyal connective tissue and are not due to primary involvement of the muscle cell itself. This view is supported by the finding of a normal creatinine coefficient, an index of total muscle mass.[165]

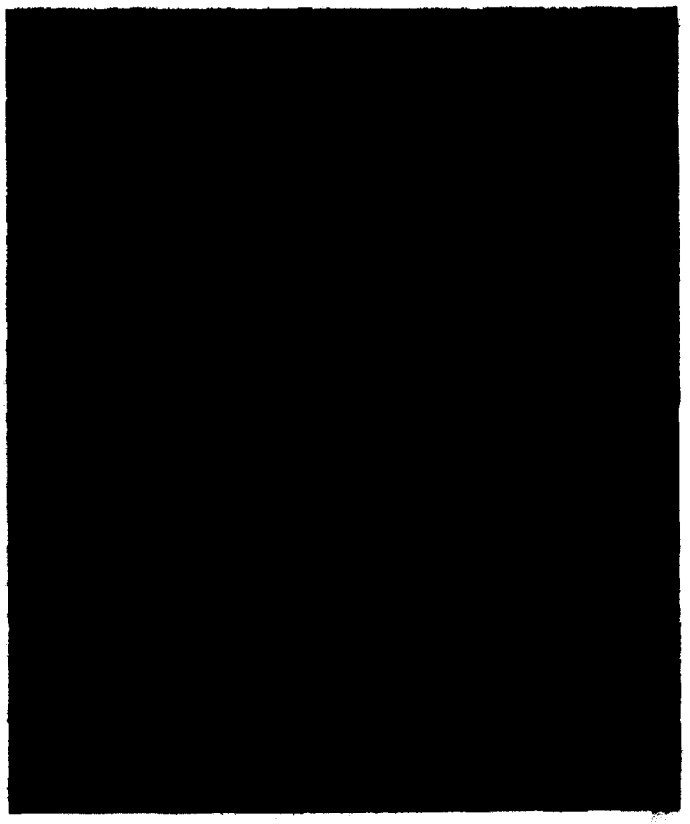
Pronounced sparsity of subcutaneous fat is a striking feature of most cases (Fig. 1,*A* and *B*) and is not easily reconciled with a fundamental defect of connective tissue. In children, it may be that the rapid growth accounts for the failure to store fat. One patient, who was thin as a child, has become exceedingly obese in recent years (she is now 25 years old), due in large part to inactivity associated with the blindness produced by bilateral retinal detachment (Fig. 6). As demonstrated in Fig. 1,*G*, etc., others of these patients may have abundant subcutaneous fat.

The Eye.—Ectopia lentis, almost always bilateral, is the hallmark of ocular involvement in this syndrome (Fig. 5). The suspensory ligaments, when visualized with the slit lamp, are redundant, attenuated, and often broken. The lower ligaments are more likely to be defective with displacement of the lens upward as the usual finding. The lens is often abnormally small[49,87,88] and spherical.

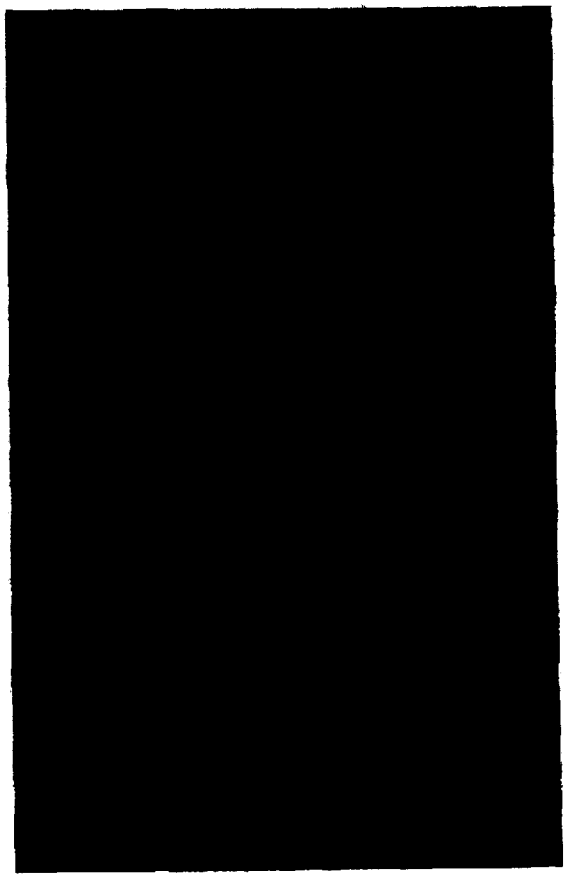
Myopia is usually present in rather high degree. The excessive length of the eyeball, resulting in myopia, appears to indicate involvement of the sclera, fundamentally a ligamentous structure, in the basic connective tissue defect. The scleral defect is occasionally expressed in the cornea as keratoconus or as megalocornea.[151]

*In one case,[14] a peculiar pelvic cyst communicating with the lining of the sacral canal occasioned difficulties in delivery.

1,*A*.

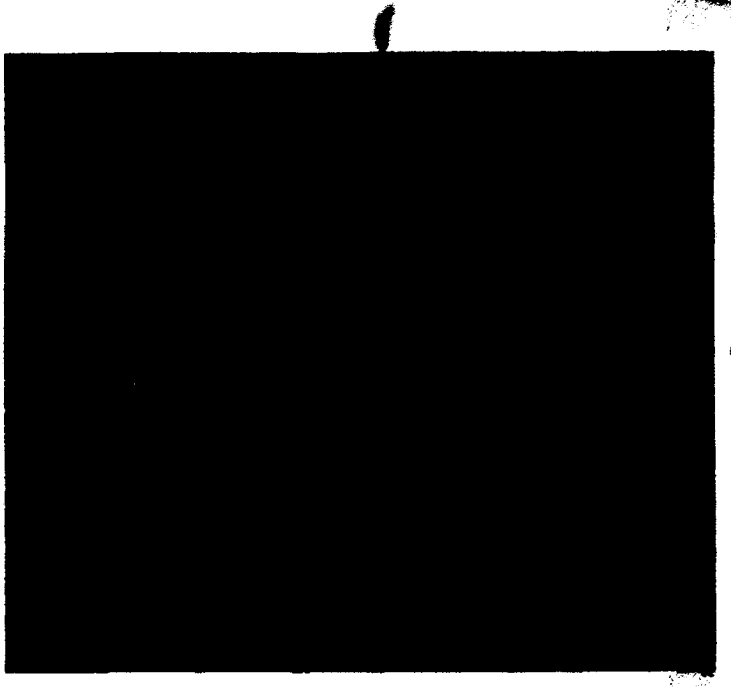


1,*B*.



1,*C*.

1,*D*.



1,*E*

Fig. 1,*A*.—Brothers, one with Marfan's syndrome. The one on the left is normal, aged 10 years. M.D. (A 59949), on the right, is only 8 years old. He shows ectopia lentis, contracture of the fifth fingers (see Fig. 3,*C*), heterochromia iridis (right iris, blue; left, light green), Horner's syndrome on left, lack of subcutaneous fat, high palate, scoliosis and thoracic deformity, abnormal electroencephalogram. This is probably a sporadic case (original mutation). Contracture of the fifth fingers (clinodactyly or camptodactyly) occurred in other patients of this series (e.g., J.A.M., A 65283).

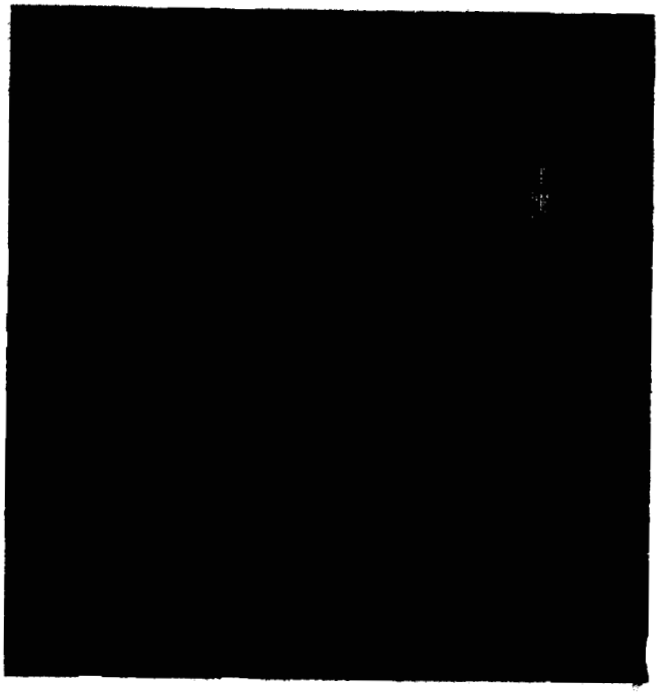
Fig. 1,*B*.—C.A. (B 9912; 692938) 7 years old. Pronounced pectus carinatum. Normal mentality. Nystagmus. Bilateral ectopia lentis. "Rocker-bottom" feet. Sparce subcutaneous fat.

Fig. 1,*C*.—M. McG. (A 92675), aged 7 years. Bilateral ectopia lentis. Severe pectus excavatum. Highly intelligent. Frequent respiratory infections. Loud systolic murmur of unclear origin. The mother has the full-blown syndrome and is sightless in one eye from spontaneous retinal detachment.

Fig. 1,*D*.—D.W. (B 8430), 50 months old. Is thought to have minimal dilatation of the ascending aorta and mitral regurgitation. Also has kyphoscoliosis and ectopia lentis. Parents appear unaffected but paternal great grandfather was 6 feet 7 inches tall.

Fig. 1,*E*.—M.P. (362804), 53 years old, the oldest patient with the Marfan syndrome I have had opportunity to examine. (One man with probable Marfan's syndrome was killed accidentally at the age of 82 years. He was still well preserved at that time. He was 75 inches tall and fathered at least two full-blown cases of Marfan's syndrome [see Fig. 2 of reference 92 for the x-ray of one] and four probably affected individuals out of sibship numbering twelve in all.) Extensive pedigree of Marfan's syndrome. Systolic crunch (extracardiac sound) present for many years.

1,*F*.



1,*G*.

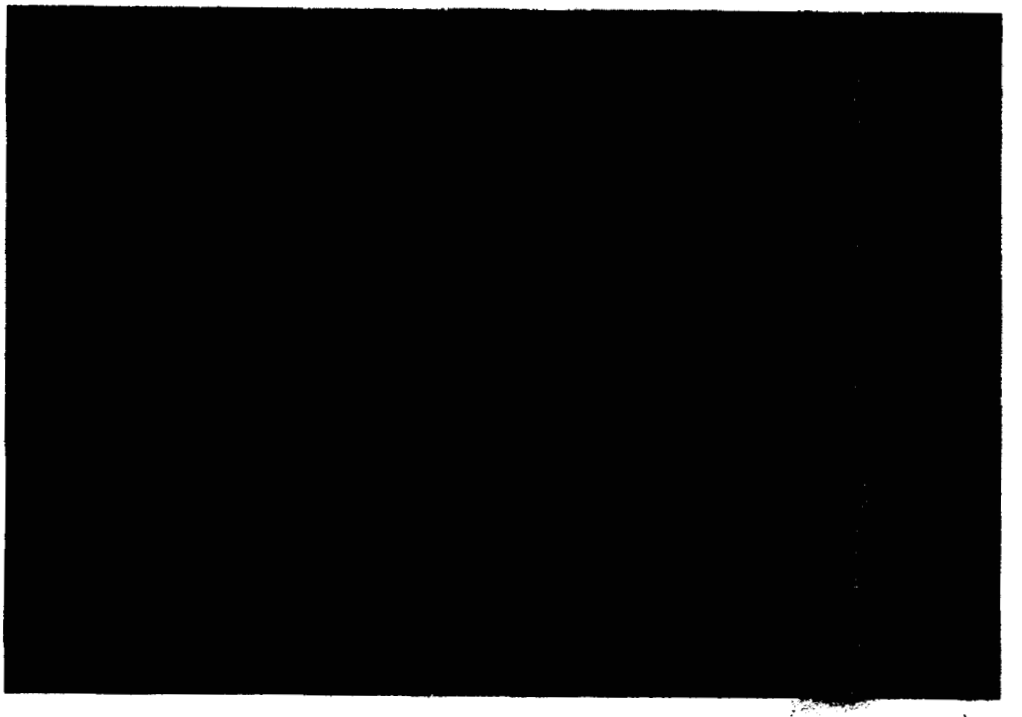


Fig. 1,*F*.—D.L.F. (516670), aged 7 years. The ptosis was thought to be part of the general muscular hypotonia which was so severe that amyotonia congenita was suspected when the patient was seen at the age of 4 years. Umbilical and bilateral inguinal hernias have been repaired surgically. The feet are very long, flat, and narrow. Kyphoscoliosis is evident. No ectopia lentis or ocular abnormality other than ptosis demonstrated. Intelligent.

Fig. 1,*G*.—J.A.L. (661948), aged 5 years, 8 months. Ectopia lentis. Probably *de novo* mutation. Shown very well is the eversion of the feet with low position of the internal malleolus ("rocker bottoms"). Child bright, but highly nervous.

The sclera may be impressively blue in the Marfan syndrome.[23] Clouding of the cornea occurs occasionally. How much of this is a primary element of the connective tissue disease and how much a result of the secondary iritis and glaucoma is difficult to state.

Spontaneous retinal detachment occurs with what is probably an unusually high incidence and is a frequent complication of lens extraction. Retinal detachment is probably related to the long myopic eyeball and therefore indirectly to the connective tissue defect; that there is a more direct relationship is strongly suspected[72] because of the high incidence in Marfan's syndrome even without more than a moderate degree of myopia. The pupil is often difficult to dilate in Marfan's syndrome and the dilator muscle appears to be hypoplastic.[137]

The ectopia lentis per se would probably represent relatively little impairment of vision. The severe myopia (20 diopters in Boerger's[24] case), the retinal

A. B. C.

Fig. 2.—Confusing and uncertain cases.

A.—L.M. (611512), 45-year-old Negro man, sustained an injury to his chest one year before this photograph. Shortly after the accident he began to have paroxysmal nocturnal dyspnea and was found to have profound aortic regurgitation. The left ventricle and first portion of the ascending aorta are enlarged. Spinal deformity has become progressively more impressive in this patient. There is no ectopia lentis. For geographic reasons, the family investigation is not entirely satisfactory, but no suspicions of the Marfan syndrome are present on this score either.

B.—W.F. (651498), 12 years old. Two years previously acute encephalitis occurred, followed by mental deterioration with positive neurologic signs. No ectopia lentis. The mother, who is normal, has the same skeletal proportions.

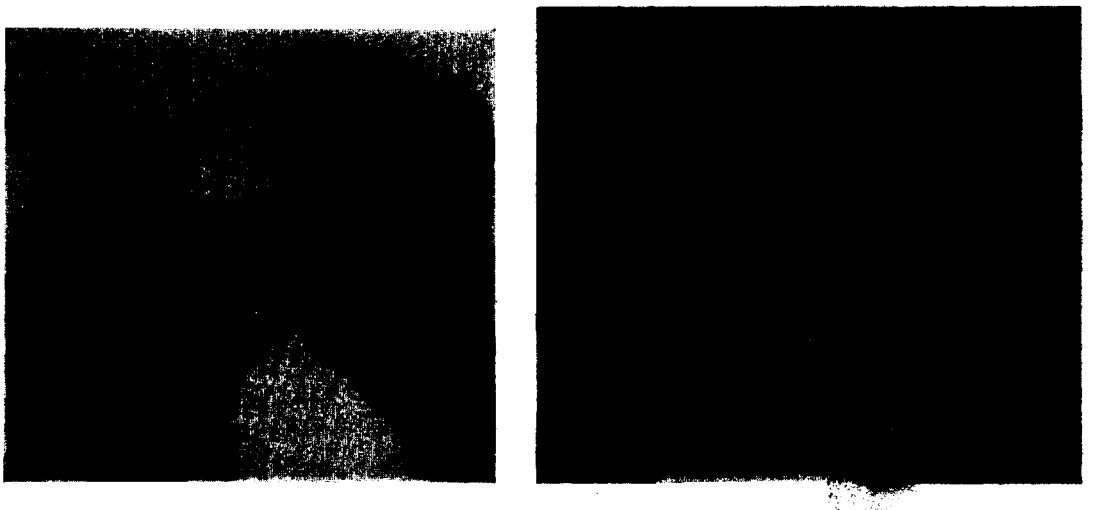
C.—R.G.W. (697871), only 13 years old. Myopic astigmatism but no ectopia lentis. Loud precordial systolic murmur of unidentified cause. Cardiac catheterization unrevealing. The extreme dolichostenomelia and the pelvic asymmetry make Marfan's disease very likely. The diagnosis cannot be established in the absence of positive family history or ectopia lentis.

detachment, and the iritis and/or glaucoma which may result from the ectopia lentis are often responsible for severe limitation of visual acuity or even total blindness. The lens may become secondarily cataractous.

I was previously suspicious that estimations that only 50 to 70 per cent of cases of clean-cut Marfan's syndrome have ectopia lentis were incorrectly low as a result of inadequate examination of the eyes and that virtually 100 per cent of cases would display at least minor redundancy of the suspensory ligament if subjected to maximal mydriasis and slit-lamp examination. It may be true that the first estimate above is too low. We have now observed patients with

A. B.

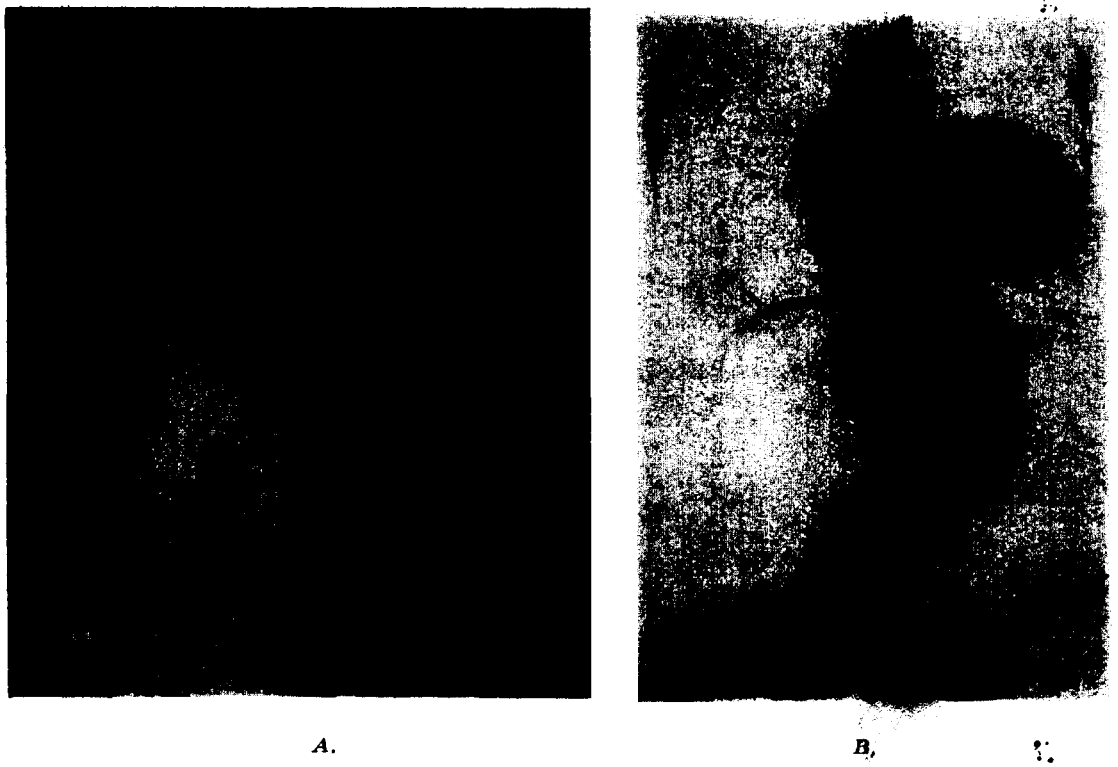
Fig. 3,*A* and *B*.—H.W. (464314), 17 years old. *A*, Died suddenly at home eighteen months after this picture. Ectopia lentis. Referred because of spontaneous retinal detachment. Striking arachnodactyly with partial contractures of fingers. Children delight in doing contortions with their fingers but should not be permitted to do this since they probably do themselves harm thereby. *B*. Extraordinary length of the great toes is well demonstrated. Even more pronounced excess of length of great toe shown by case illustrated by Whitfield, Arnott, and Stafford.[180]



C. D.

Fig. 3,*C*.—Flexion deformity (clinodactyly) of fifth fingers, particularly on left. Taken at age of 38 months in M.D. (A 59949), who is shown at a later age in Fig. 1,*A*. Other patients in this series have shown this feature.

Fig. 3,*D*.—X-rays of feet in case with so-called "rocker bottoms", i.e.; pronounced flat feet. Patient J.M. (544088); see also Fig. 12.



A. *B.*

Fig. 4,*A*.—Asymmetrical pigeon-breast type of chest deformity in 14-year-old boy (J.S., 543026) with full Marfan's syndrome. This particular type of anterior chest deformity seems to be of frequent occurrence in Marfan's syndrome. At the age of 18 years, the patient was 73 inches tall. Incomplete right bundle branch block is present. The patient's father was 6 feet 7 inches tall, and at the age of 28 years died suddenly on a street bus. He had been observed for two years for aortic regurgitation which had been considered rheumatic in origin.

Fig. 4,*B*.—Marked spinal deformity in 14-year-old F.D., one of first cases of aortic aneurysm with arachnodactyly reported by Baer et al.[11] (See reference 11 for photographs of the external appearance of this patient.)

Fig. 5.—Dislocated lens in R.C. (241676), then aged 6 years. Chronic "malnutrition," bilateral inguinal hernias, slow physical development, diastasis recti. At the age of 22 years he was 73 inches tall, weighted 150 pounds, and wore a size 12 AAA shoe. He was inducted into the army and served six months before his eye condition was ascertained. The slight divergent strabismus is evident. Also one can make out the forward bulging of the nasal portion of the right iris with failure of more complete dilatation of the pupil in that segment because of anterior synechiae.

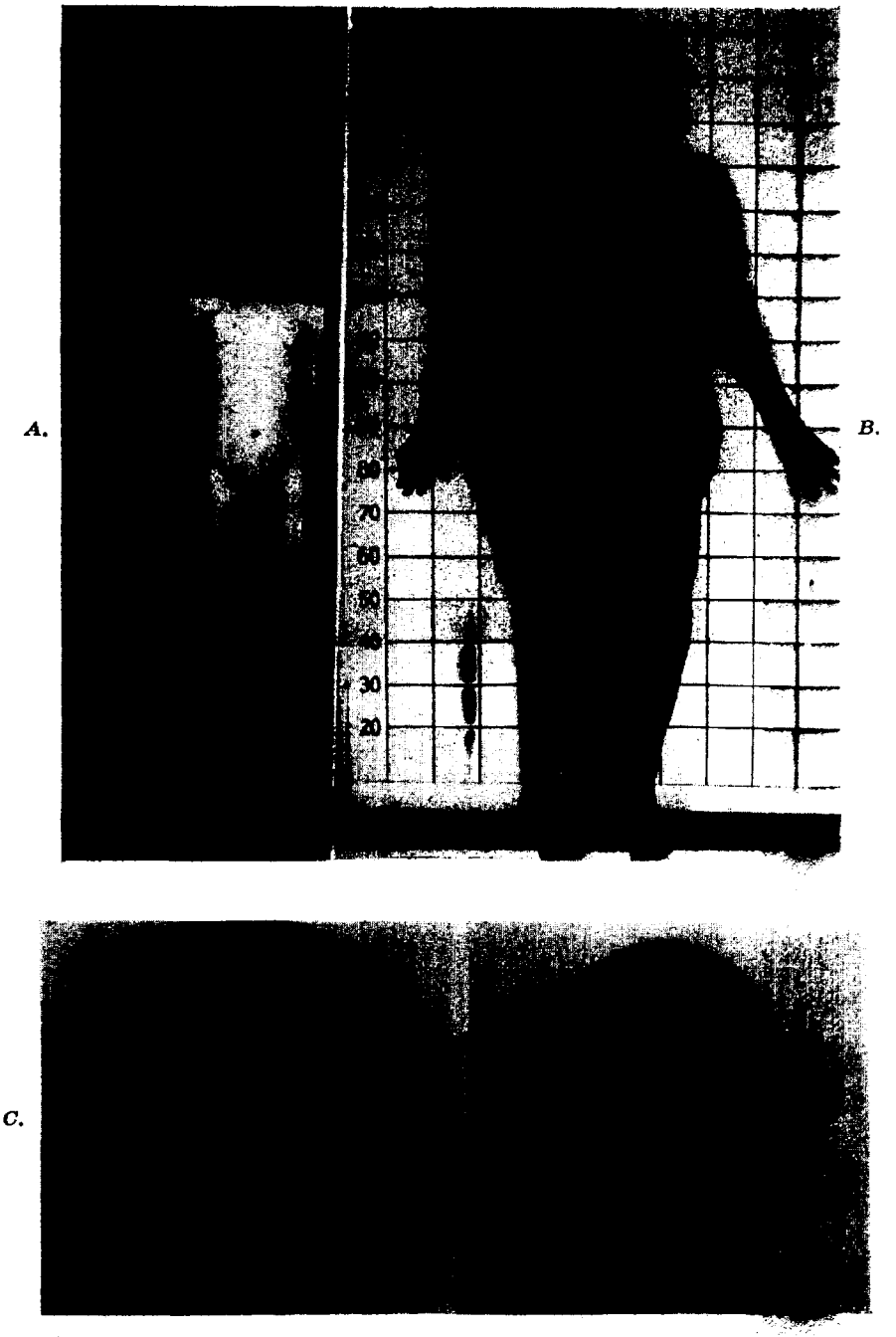
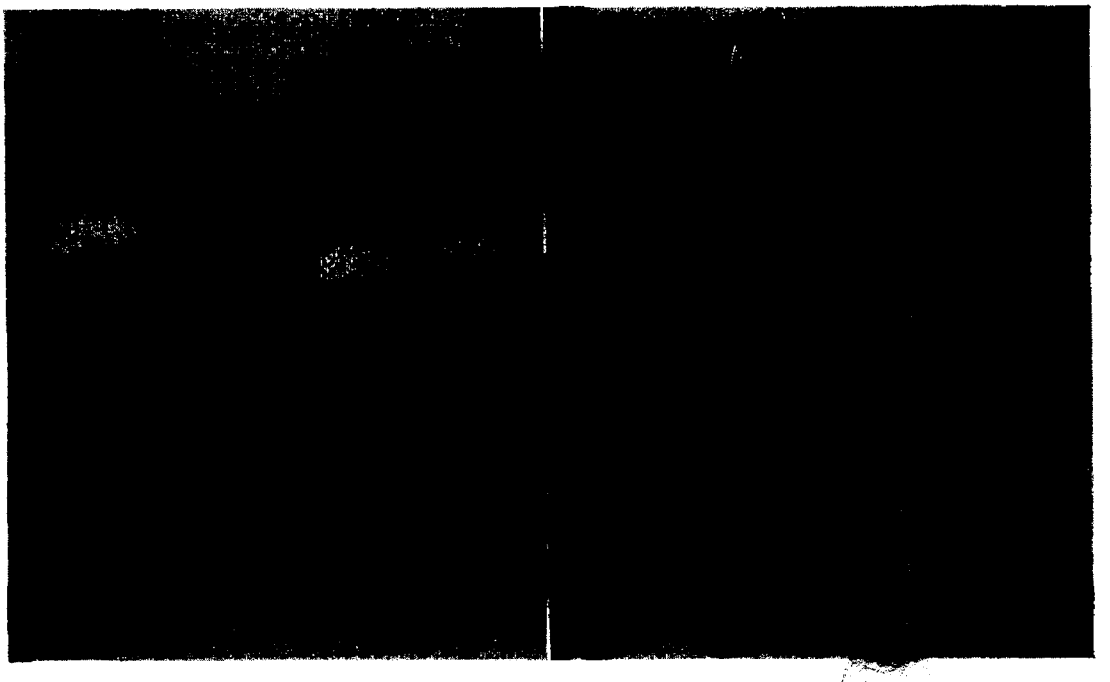


Fig. 6.—L.T. (221183), at the age of 8 years (*A*), at the age of 23 years (*B*), At 8, the patient is virtually the same height as M.D. (in Fig. 1,*A*), also 8 years old. The patient became almost completely blind from bilateral retinal detachments. With the inactivity associated therewith, she became very obese, as demonstrated in *B*. White atrophic striae appeared on the shoulders, upper arms, hips, and thighs, as has been described previously in obese patients with Marfan's syndrome.[73] The patient probably had rheumatic fever with carditis as a child, but no residua are detectable. She has demonstrated, in addition to ectopia lentis, accessory rudimentary sixth digit bilaterally, highly arched palate, pupils which react poorly to mydriatrics. *C*, Prison photograph of the proposita's father (B.R.). The character of the spectacles suggests hyperopia, an unusual although occasional finding in the Marfan syndrome. He had several admissions to the Norfolk, Virginia, General Hospital (A 16772) for hernia repair, for acute dissection of the aorta (age 38), for varicose veins, for pain in the low back. The final hospital admission was to the St. Luke's Hospital, Newburgh, New York, because of severe pain up and down his back. Profound aortic regurgitation and a pulsating abdominal mass were discovered. Serologic tests for syphilis were negative. The patient died suddenly (age 39). Autopsy revealed old dissection of the aorta with recent rupture into the pericardial cavity and tamponade.

advanced Marfan's disease with characteristic habitus, involvement of other members of the family, and dissection of the aorta with autopsy demonstration of pathognomonic changes in the media, who did not have ocular abnormality on most careful examination. This part of the syndrome, it seems, may be suppressed in a given family. This is consonant with the frequent observation that the pattern of expression of this syndrome seems to be similar in affected members of one kinship.



A. *B.*

Fig. 7.—In *A* and *B* are shown a normal individual (III 12) and her five siblings affected by the Marfan syndrome (III 15, III 14, III 13, III 11, and III 8). Also shown in *B* is a 4-year-old affected member (IV 13) of the next generation, son of III 8. (The numbers refer to those in a pedigree published elsewhere.[92]) Individual III 11 subsequently died of bacterial endocarditis engrafted on a mitral valve probably affected by connective tissue changes of the Marfan syndrome.[92] There was chromatropic degeneration of the ascending aorta and pulmonary artery as well as advanced congenital cystic disease of the lungs. Individual III 14 is 78 inches tall. (History numbers: 176836, 176837, 176838, 103632, 637693, 637694, 392843.) The father of the sibship shown in *A* and *B* (W.R., 401043) died suddenly at home at the age of 43, presumably of aortic rupture. He was well known as a case of Marfan's syndrome and had been under treatment for a cardiac ailment with aortic regurgitation for about two years.

The Cardiovascular System[61,92].—Since most of the early autopsies in cases of this syndrome were in infants and children, and since interatrial septal defect was found (probably largely by coincidence) in several of the cases, this malformation and "congenital heart disease" in general came to be considered the usual form of cardiovascular involvement. As more adult cases were recognized, it became apparent (1) that an inborn weakness (with subsequent degeneration) of the media of the aorta and main pulmonary artery is of much more statistical importance and more functional importance in the individual patient, and (2) that this abnormality is an abiotrophy, not a congenital malformation. The abnormality of the media may result in diffuse dilatation of the ascending aorta or pulmonary artery, in dissecting aneurysm, or in a combination of dilatation and dissection. Striking involvement of the pulmonary artery occurs[11,92,166] much less commonly than the corresponding involvement of the

aorta. However, a clinical picture like that of so-called[77] "congenital idiopathic dilatation of the pulmonary artery" may occur, as well as dissecting aneurysm of the pulmonary artery.[5,182]

In the aorta, dilatation usually begins in the aortic ring and intrapericardial portion of the ascending aorta as suspected clinically and as demonstrated in cases dying before further progression of their disease.[91,175] This, together with stretching of the aortic cusps, may produce profound aortic regurgitation before clear roentgenologic signs of aortic dilatation are present (Figs. 8,*D*, 12,*C*, and 13). If syphilis, rheumatism, and bacterial endocarditis can be excluded, traumatic rupture of an aortic cusp is often suspected.[15,93]

Furthermore, a deceptive prominence of the pulmonary conus and main pulmonary artery may be produced by the dilated aortic base and compound the confusion.[11,92,112] In a recent case (J. M., J. H. H. 544088) the aneurysm at the base of the aorta apparently caused partial obstruction of outflow from

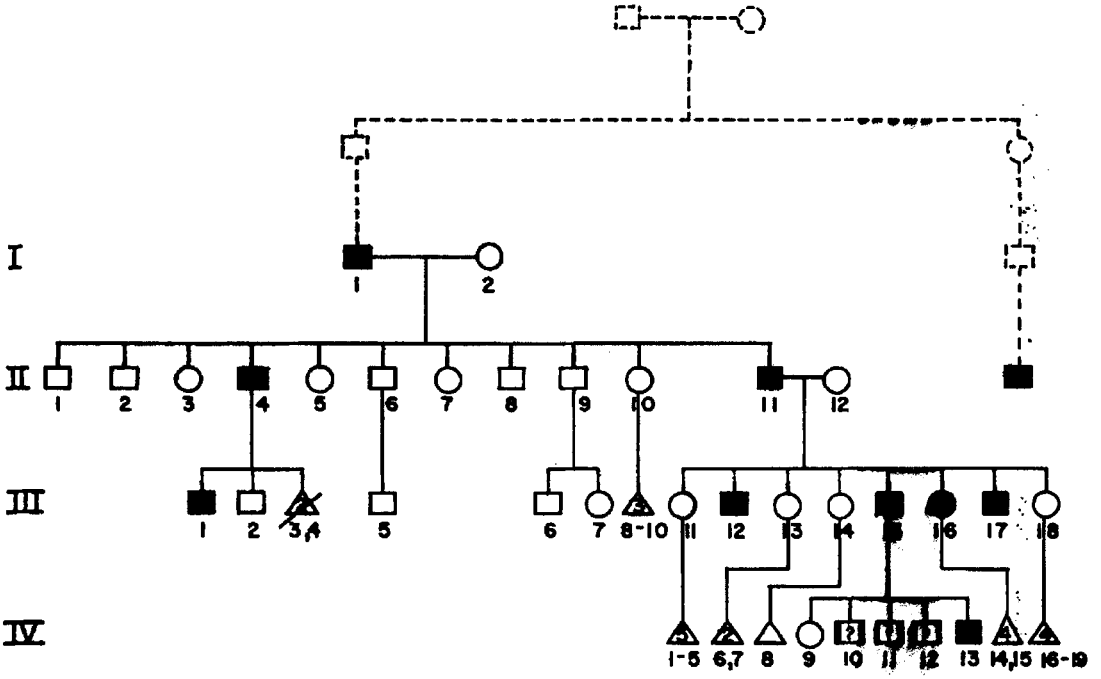


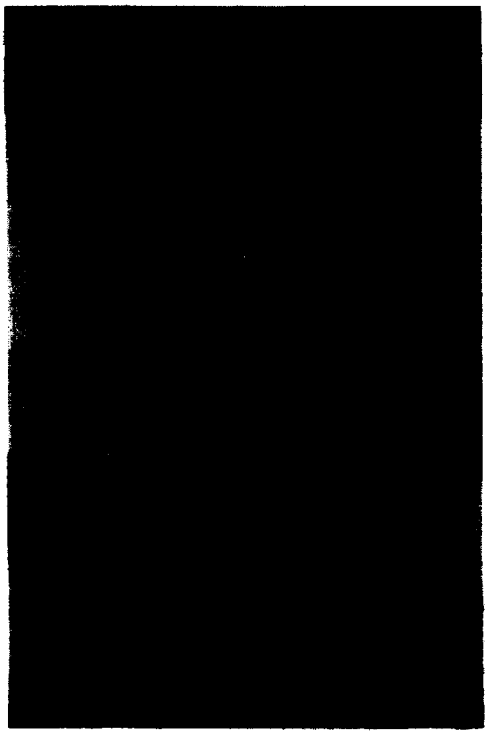
Fig. 8,*A*.—Pedigree of the F. kinship.

II. 1. Charles. Died of acute indigestion at age 47. 4. Grant. About 6 feet 4 inches tall, died at age 35; two of his children died at 8 and 12 months, respectively. 8. Henry. Examined; unaffected.

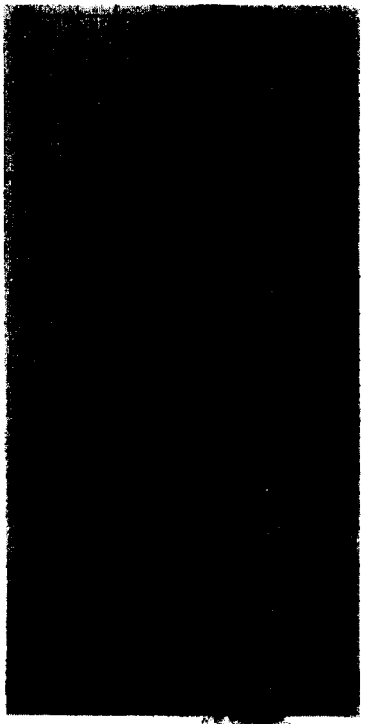
III. 1. James Aloysius. Typical Marfan syndrome; 6 feet 4½ inches tall, size 13 shoe; ectopia lentis with secondary cataract formation; complete loss of vision from bilateral detachment of retina; early aortic diastolic murmur. 11. Josephine. Examined; unaffected. 12. Clarence (352936). At age of 32 years found to have complete detachment of right retina; left lens dislocated and cataractous; partial detachment of left retina; died at age of 34 years, 18 days after onset of congestive heart failure attributed to syphilitic heart disease because of finding of aortic regurgitation. 13. Blanche. Examined; unaffected. 15. Theodore (see Fig. 8,*B*). Typical Marfan syndrome with cardiovascular death. 16. Leona (see Fig. 8,*C*, *D*, and *E*). Typical Marfan syndrome with autopsy confirmation of dissecting aneurysm of the aorta. 17. James Leon (424834). Ectopia lentis with severe secondary iridocyclitis and glaucoma; detachment of right retina; 75 inches tall, weight 172 pounds, kyphoscoliosis, variococele; lax sternocleidomastoid joints, mobile patellae, flat feet, cardiomegaly with globular shape by x-ray; no murmurs. This individual and Theodore and Clarence "always looked just like twins." Positive serologic test for syphilis.

IV. 9. Mary, b. 1939, probably normal. 10. Leroy, b. 1940, probably normal. 11. James, b. 1944, peculiar shape of head. 12. Edward, b. 1945. Same peculiar shape of head. 13. D. Theodore. b. 1950. Definite Marfan syndrome: 38 inches at 30 months; long peculiarly shaped head.

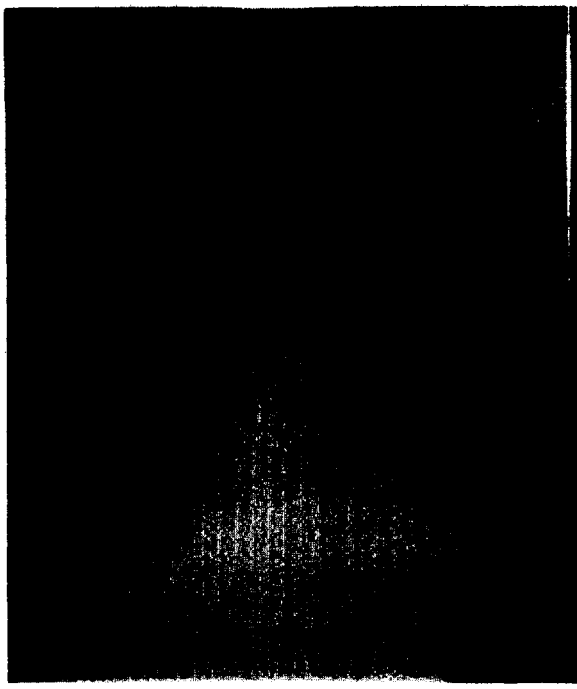
8,*B*.



8,*C*.



8,*D*.



8,*E*.

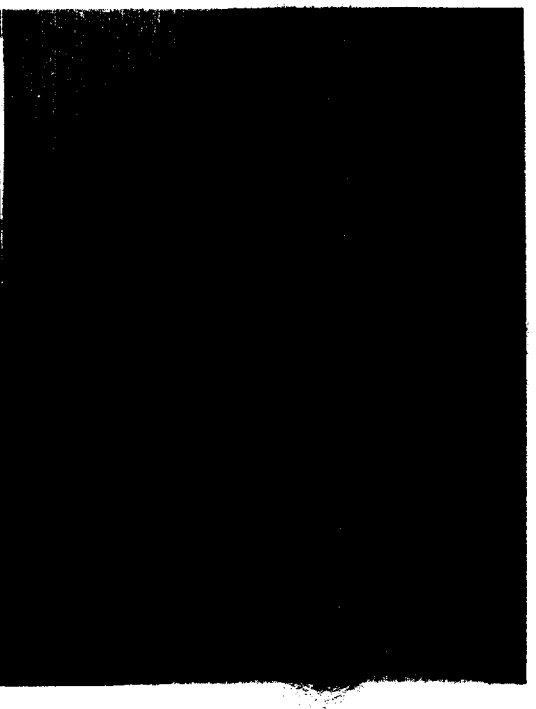


Fig. 8,*B*.—Carnival snapshot of III 15 (T.F.). Arachnodactyly is evident. In his left hand he holds his spectacles. He died suddenly at the age of 33 years, two weeks after consulting a physician for exertional dyspnea. Aortic regurgitation had been discovered. An optometrist reports that he had "a decided miosis and the opthalmoscopy showed the media to be cloudy." He was myopic. Worked as farm laborer until a few days before death.

Fig. 8,*C*.—L.F.Y. (690823), 33 years old. Patient died of effects of severe aortic regurgitation. Autopsy revealed characteristic changes in the media of the aorta and pulmonary artery with old dissecting aneurysm of the ascending aorta. (See Fig. 14B, in reference 96 for a drawing of the aorta with old dissecting aneurysm.)

Fig. 8,*D* and *E*.—Posteroanterior and lateral views of chest in L.F.Y. It is remarkable that enlargement of the aorta is not more evident. In lateral view there is opacification behind the sternum.

the right ventricle with the development of progressive right axis deviation by electrocardiogram. In these cases, the second heart sound in the pulmonary area may be unusually loud due to close proximity of the pulmonary artery to the anterior chest wall.

Aortic dilatation is usually progressive. The patient may be free of symptoms for five or more years after the development of aortic regurgitation, but once angina pectoris or symptoms of left ventricular failure have developed, he seldom lives more than two years. On the whole, the prognosis is quite similar to that of syphilitic aortitis.[174] In fact, the similarities of the two diseases are in many respects striking. It seems to matter little whether the defect of the media, specifically the elastic lamellae, is produced by the spirochete from without or the mutant gene from within.

The onset of aortic dilatation may be as early as the fifth year or as late as the sixth decade. The oldest reported patient with aortic insufficiency without

A. *B.*

Fig. 9, *A* and *B*.—Fourteen-year-old S.S. (366788), II 6 of the pedigree (*C*), and her normal 12-year-old brother, II 7. Note the kyphoscoliosis, genu recurvatum, excessively long legs, strabismus. Ectopia lentis is present.

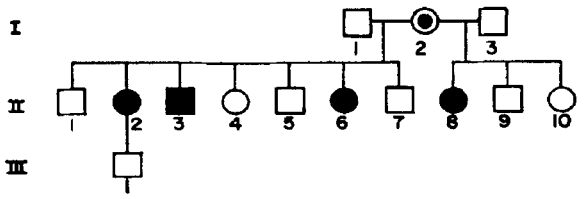


Fig. 9, *C*.—This pedigree illustrates how submerged the manifestations of Marfan's syndrome can be. Individual I 2 had had at least three affected offspring by one husband and one affected offspring by a second husband. Both husbands are unequivocally normal from the skeletal, ocular, and vascular points of view. The mother is 5 feet 8 inches tall, is moderately long of limb, is poorly muscled, and is severely myopic (6 D.), but has no ectopia lentis by careful ophthalmoscopic examination. (For the last I am indebted to Dr. J. E. Mishler of Atlantic City, N. J.). These manifestations are consistent with *forme fruste* of the Marfan syndrome but would not be recognizable as such without the knowledge of this pedigree.

evident aortic dilatation was 56 years of age.[76] In one reported case,[162] dilatation of the ascending aorta with aortic regurgitation and marked left ventricular hypertrophy resulted in the death of a 10-month-old infant; in another case,[146] death occurred at 55 years.

The dilatation is almost always confined to the ascending aorta proximal to the innominate artery. However, in Case 3 of Thomas and co-workers,[159] the descending aorta was also involved. Furthermore, at least two instances of fusiform aneurysm of the abdominal aorta have been described recently.[82] Dissection exclusively in the aorta beyond a mild coarctation at the usual site has been described.[168] Several cases (e.g., reference 106) have had cystic medial necrosis, dissection, and internal tears in the abdominal as well as the ascending aorta.

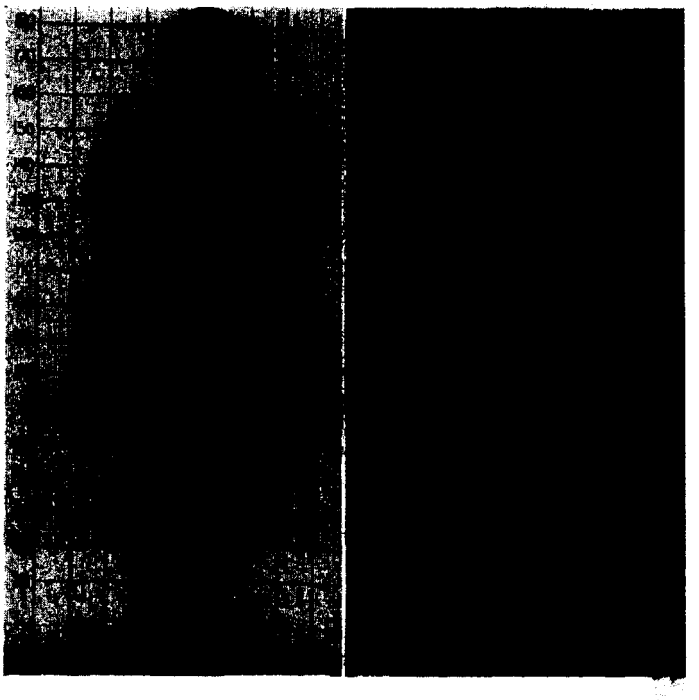
Fig. 10. Fig. 11.

Fig. 10.—C.H. (687485), 28 years old. Ectopia lentis. Lenses correcting for aphakia worn from age of 5 years. Brother, father, two paternal aunts, and two cousins are living and have the Marfan syndrome. Paternal grandmother and great grandmother likewise had it. Father blind in both eyes and aunt blind in one eye from secondary glaucoma. Patient in Army for 45 months. Note deformity of knees. This and many of the other members of this group of photographs makes it clear that on superficial inspection the habitus may not seem impressively or abnormally dolichostenomelic.

Fig. 11.—Father, E.C., and two children, Anna (593933), aged 9 years, and Robert (441759), aged 7 years, all with ectopia lentis and skeletal proportions, albeit not striking, consistent with the Marfan syndrome. The father's brother had had a "leaky heart" for several years and died suddenly at the age of 35 years.

By examining a large number of patients with ectopia lentis and by studying the relatives of established cases of Marfan's syndrome, we have now discovered five patients who appear to be in the early stages of aortic dilatation with aortic regurgitation.[92] In none is there yet evident dilatation of the ascending aorta (Fig. 13).

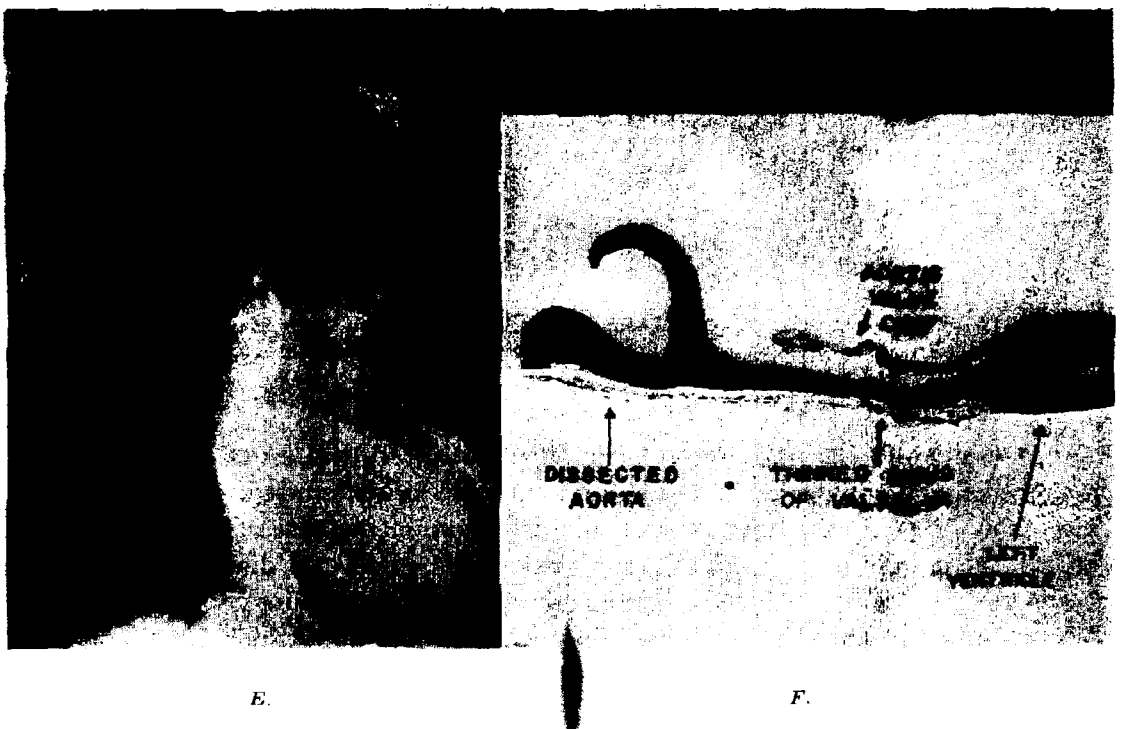
Dissecting aneurysm may occur as the first aortic complication or may be superimposed on diffuse dilatation of the ascending aorta.[98] There is evidence that dissection may occur in the first decade of life; the oldest reported case of dissecting aneurysm in Marfan's syndrome was that of a 52-year-old woman.[48] The patient may survive for a number of years after first dissection of the aorta and even after a "leak" into the pericardium. Because of the aortic regurgitation which results either from the dissection itself[64,127] or from the associated dilatation of the aortic ring, confusion with rheumatic[83] or syphilitic[60] heart disease is frequent. In a recently autopsied case at this hospital, leaking of the original dissecting aneurysm into the pericardial sac led to the misdiagnosis of tuberculous pericarditis. The patient survived five years after the first pericardial episode. Dissection apparently occurs with increased frequency during pregnancy.[107,141,143] In chronic dissecting aneurysm of the aorta, there may be little enlargement of the aorta evident on x-ray (see Figs. 8 and 12). In our experience, when full family investigations are made, Marfan's syndrome is found to be the leading "cause" of dissecting aneurysm in persons under the age of 40 years. Gore[57] reported that 3 of 22 cases had arachnodactyly. This, however, was not a detailed clinicogenetic study.



A. *B.*

Fig. 12,*A* and *B*.—Brothers with the Marfan syndrome without ocular manifestations. *A*, J.M. (544088) had genu valgus, severe pes planus, dolichostenomelia but no ectopia lentis. In 1950 an episode of chest pain accompanied by pericardial friction rub was interpreted as pericarditis and treated for presumed tuberculous etiology. Signs of aortic regurgitation developed thereafter. In 1953, there occurred at least one other episode of chest pain with pericardial friction rub. The effects of aortic regurgitation became progressively more severe and were the cause of death in April, 1955, at the age of 30 years. Autopsy revealed superannuated dissecting aneurysm of the ascending aorta and dilatation of the aorta above the aortic ring. The aorta had apparently "leaked" into the pericardial sac almost five years before death. (Known to us is a second case [S.T., 691351] in which the patient was still living following leakage about 18 months before. The diagnosis of Erdheim's disease was established at operation for aneurysm of the ascending aorta.) *B*, W.M. (702409), aged 27 years, was discovered to have aortic regurgitation when examined in connection with his brother's illness. He had dolichostenomelia and spinal curvature. Although the left ventricle is large, no dilatation of the aorta is demonstrable. He is asymptomatic.

C. D.



E. F.

Fig. 12,*C*—*E*.—Series of x-rays in J.M. *C*, Taken in 1950 about one month after the initial episode of leakage into the pericardial sac. *D* and *E*, The appearance in the last year of life. Enlargement of the aorta is not impressive in *D*, but the main pulmonary artery is prominent. In the right anterior oblique (*E*) the barium-filled esophagus is displaced by a structure which necropsy demonstrated to be an aneurysm of the sinus of Valsalva. In the left anterior oblique (not shown here), again the aorta does not appear particularly dilated.

Fig. 12,*F*.—Microscopic section (×4) of aortic valve area in J.M. (see *A*). The old dissection, the thinning of the sinus of Valsalva, and the minor fibrous thickening of the aortic valve are demonstrated.

Involvement of the aortic cusps has already been described. The mitral cusps and chordae tendineae may be redundant with resulting mitral regurgitation. Subacute bacterial endocarditis may become engrafted on the valvular abnormality.[92,108,170] Murmurs of obscure origin are frequently encountered. Some may be on the basis of redundant chordae tendineae with incompetence of atrioventricular valves. Extracardiac clicks and other extraneous sounds are frequent because of the thoracic deformity.

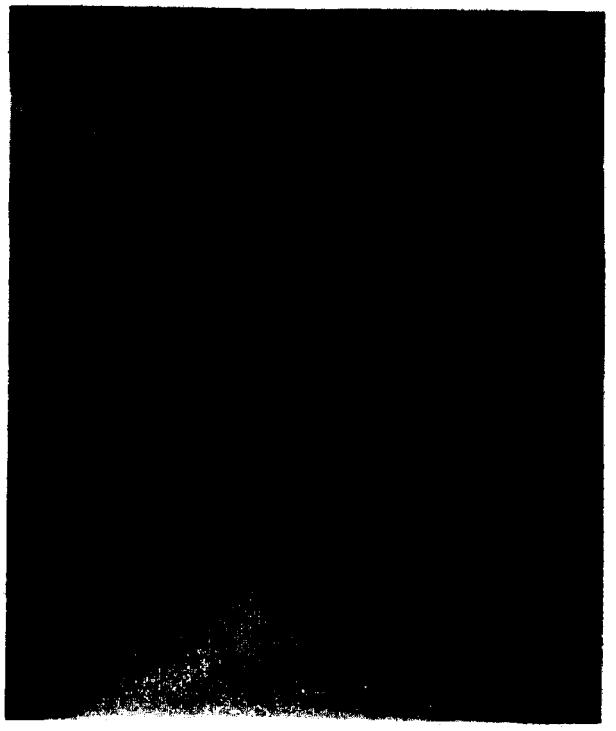


Fig. 13—X-ray of chest in M.B. (697662), 46 years old. Ectopia lentis, moderate dolichostenomelia, spinal curvature. Although the patient is asymptomatic and the cardiovascular silhouette is normal, an aortic diastolic murmur is present.

Occasionally the pathophysiologic effects of interatrial septal defect dominate the clinical picture. Notwithstanding careless statements of previous reviews, no autopsy-confirmed or even clinically convincing case of interventricular septal defect has been reported. In Cockayne's case[33] the diagnosis was only suspected clinically. There is a report[86] of possible tetralogy of Fallot with Marfan's syndrome. In two cases of tetralogy of Fallot which have come to my attention,[92] there are stigmata suggestive of the Marfan syndrome, but the absence of involvement of other members of the family and the failure of ectopia lentis to be found in the patients make the diagnosis of the Marfan syndrome uncertain. I am inclined to think that these are not cases of the Marfan syndrome. In yet another case (Fig. 16), striking dolichostenomelia, congenital clouding of the cornea and large interventricular septal defect are associated. Four siblings, two older and two younger, are unaffected as are all other members of the family, in so far as can be determined. Furthermore, no abnormality of the lens is detectable. This case seems most likely the result of infection or other abnormality of the intrauterine environment.

Much has been written about cardiac disability in pectus excavatum.[45,48,104,157] Furthermore, since originally proposed by Flesch[50] in 1873, excessive longitudinal growth of the ribs has been thought to be the mechanism in many cases. As stated above, this appears to be the pathogenesis of the pectus excavatum in the Marfan syndrome. The hereditary nature of pectus excavatum has been appreciated.[114,135,147,153] Many times the patients with pectus excavatum are described as being unusually tall and thin with spinal curvatures. Despite all these considerations, it has not been properly appreciated that the pectus excavatum may be but one manifestation of a generalized disorder of connective tissue in which direct involvement of the cardiovascular system may occur. Elsewhere,[92] we have presented the case of a 24-year-old man with severe pectus excavatum, who died of rupture of the aorta shortly after surgical repair of the chest deformity.[21] Autopsy revealed aortic changes typical of the Marfan syndrome. An aortic diastolic murmur had been present before operation.

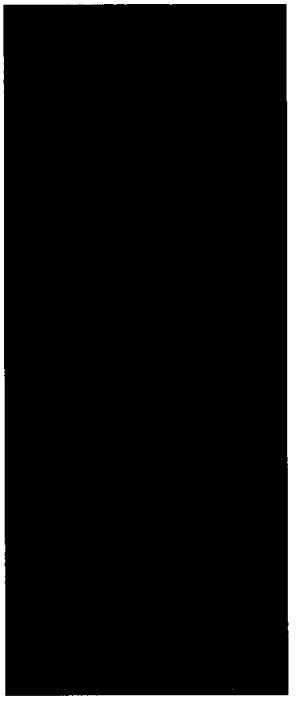


Fig. 14.—The patient, R.R. (704121), aged 30 years, has clouding of the cornea, dolichostenomelia, and probable large interventricular defect. It is likely that this is due not to Marfan's syndrome but rather to intrauterine insult of unidentified variety.

In the surgical literature, there are two cases which may have been instances of the Marfan syndrome. One patient[83] was 6 years old and was described as having "systolic and diastolic murmurs and cardiac incompetence." The other,[125] 23 years old and 74 inches tall, had congestive heart failure and atrial fibrillation and was specifically described by his physician as thin, gangly, loose-jointed, and round-shouldered. In another instance, a case reported by Sweet,[158] the patient has been discovered to have typical Marfan's syndrome.[179]

The cardiovascular aspects of this syndrome have been presented in greater detail elsewhere.[92]

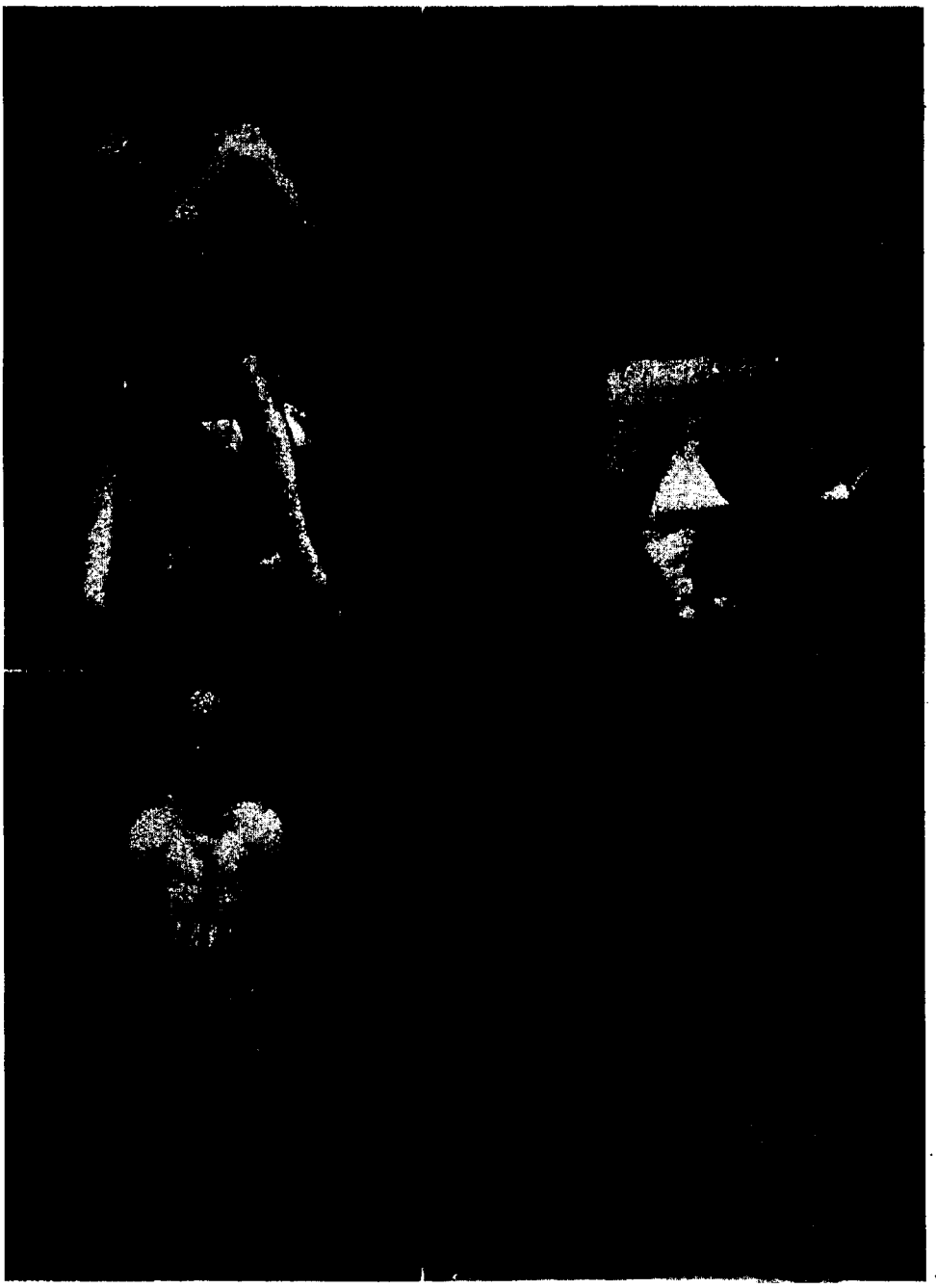
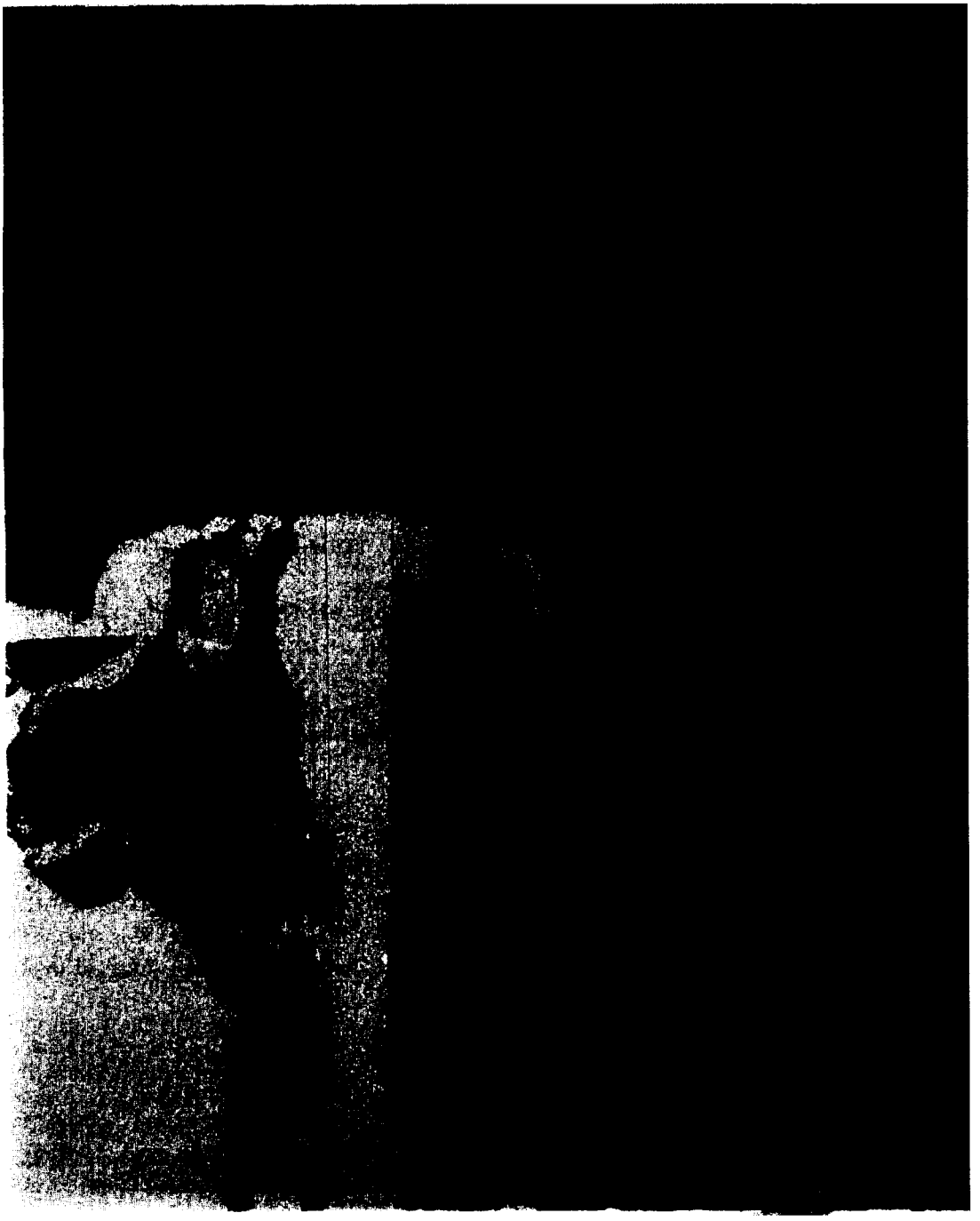


Fig. 15.—*A* and *B*, W.M. (Mary Imogene Bassett Hospital No. 54659) was thought to have Marfan's syndrome because of aortic regurgitation, severe spinal deformity, and arachnodactyly. Clinical evidence for bacterial endocarditis was present. At autopsy the heart lesions appeared to be rheumatic with superimposed valvular infection. (I am indebted to Dr. Jas. Bordley, III, for knowledge of this patient and permission to include him here.) Numerous pigmented nevi were present in this patient.

C and *D*, D.M., brother of W.M. The finding of muscular dystrophy in this brother makes it likely that W.M. (in *A* and *B*) likewise had muscular dystrophy. The disease trait appears to be recessive in this family. In D.M. note the wasting of the upper arms, especially the left, the asymmetry of the face in whistling, the winging of the scapulae. There is no arachnodactyly. Spinal deformity as severe as that in W.M. is sometimes seen with muscular dystrophy.[150] (The writer is indebted to Dr. Chas. Ellicott for studying this patient.)

A.



B. C.

Fig. 16.—Experiments conducted by Dr. James R. Brayshaw,[28] as student at The Johns Hopkins University School of Medicine.

A, Deformity and pathologic fracture of spine and other bones in rat fed seeds of *Lathyrus odoratus*.

B, Dissecting aneurysm of the aorta with rupture in rat fed seeds of *Lathyrus odoratus*. Shown is the dissection of the media and the large mediastinal hematoma. Elastic tissue stain. The elastic lamellae are black. (×10; reduced 1/5.)

C, Same at higher magnification. On the left below, the wall of the aorta is grossly scarred through almost its entire thickness. (×30; reduced 1/5.)

Other Manifestations.—Special attention is directed to certain manifestations which were indicated by dashed lines in the "pedigree of causes" presented elsewhere[92]: e.g., in the cardiovascular system, coarctation of the aorta,[49,92,168] patent ductus arteriosus,[9] and interatrial defect; in the skeletal system, spina bifida occulta,* hemivertebra, cleft palate[130]; in the eye, microphakia, hypoplasia or aplasia of the dilator-pupillae muscle, coloboma lentis. These are not among the more common manifestations, yet they occur sufficiently often in the Marfan syndrome to be considered more than coincidental associations. Their occurrence is difficult to reconcile with a unitary theory of a connective tissue defect unless one assumes that the presence of said defect during embryogenesis provides an abnormal environment in which these anomalies, congenital malformations in the usual sense, occur with increased incidence. In accordance with this last not improbable proposition, these particular manifestations can be considered *secondary* ones.

The coarctation has never, to my knowledge, been of functional significance. There is no reason, however, why it might not be in occasional instances. Dissecting aneurysm occurs with increased frequency in coarctation[87] and although the hypertension is doubtlessly a contributing factor, the possibility of a connective tissue abnormality being responsible for both the coarctation and the dissection must be considered.

Whether deafness is a specific manifestation of the Marfan's syndrome and if so, what its mechanism is,[87] cannot be stated at present. It is said to occur in 6 per cent of cases.[123]

Pulmonary malformations are described in autopsy reports and various pulmonary complications in clinical reports.[63,78,92,111,118,124,136,161] Repeated spontaneous pneumothorax has been described.[4,75,78]

Occasionally congenital cystic disease of the lung probably occurs as an integral part of the Marfan syndrome. In patient M. R. (J. H. H. 176836; see Fig. 7) very extensive disease of this type was discovered at autopsy. The stillborn child of this patient showed abnormal lobation of the lungs but no congenital cystic disease. Without an exhaustive review of the literature, it was possible to find three cases of cystic disease of the lung in which stigmata suggestive of the Marfan syndrome were described:

1. A 26-year-old male medical student (Case 9 in reference 111) had had three attacks of spontaneous pneumothorax. He died following an attack of severe chest pain. Dissecting aneurysm of the aorta with rupture into the pericardium was discovered. Histologically there was cystic medial necrosis. Both lungs showed diffuse cystic changes regarded as congenital.

2. A 26-year-old housewife (Case 13 in reference 111) with striking dolichostenomelia had had increasing dyspnea and, at the end of her second pregnancy, frank congestive failure. X-ray showed dilatation of the outflow tract of the right ventricle; EKG showed right axis deviation and the so-called P-pulmonale. Post-mortem examination disclosed diffuse cystic changes in both lungs and widely patent foramen ovale.

3. A 12-year-old child[132] was found at autopsy to have multiple simple cysts throughout both lungs, patent ductus arteriosus, aneurysm of the pulmonary artery, and anomalous coronary artery.

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*Encephalocele in the forehead area occurred in one patient. Internal hydrocephalus is also reported.[113,124]

Congenital cystic disease is probably a secondary component of this syndrome; i.e., the presence of the connective tissue defect during embryogenesis conditions its development but is not as directly responsible for it as for some of the other manifestations. The Marfan syndrome can join xanthomatosis[148,164] and tuberous sclerosis[18,19] in the group of systemic abnormalities associated with a type of cystic disease of the lung.

There are other manifestations which occur less frequently, often in no more than single reported cases, than those termed "secondary" above. In the case of these, it is more likely that the anomaly occurs only coincidentally with the bona fide features of Marfan's syndrome. When the case in question is a sporadic one, it may be valid to assume that the mutagenic factor might have caused more than one mutation simultaneously. Furthermore, in a given family, if the anomaly in question occurs in only one of the persons affected by Marfan's syndrome, or, better yet, if the anomaly also occurs in one or more members of the family unaffected by the Marfan syndrome, the manifestation in question should not be considered part of the Marfan syndrome.

Contrary to previous emphasis,[36,87,113,140] mental retardation is not, in my opinion, a component of this syndrome. Usually the patients are at least as bright as their siblings. Sometimes their innate intelligence is not fully realized because of the limitation of opportunities imposed by severe visual impairment and other physical handicaps. In several sporadic cases in infants and children, there may be mental retardation but this has, in my opinion, a separate basis, possibly an independent mutation. Another basis for confusion is the fact that a picture including arachnodactyly and suggesting the Marfan syndrome occurs with acquired developmental abnormalities such as rubella and other maternal illness, maternal exposure to x-ray, and rh incompatibility. These patients are likely to show mental retardation.

INCIDENCE AND INHERITANCE

The sexes are equally affected.[91,123] The aortic complications do seem to occur more frequently in men.[92] Manual labor may be responsible for this. There is no racial or subracial concentration of cases. The syndrome has been reported in Negroes,[53,92] Chinese,[31,66] Japanese,[168] Hindu,[20] and Jews.[91] It has, furthermore, been reported in natives of virtually every European country. Its incidence in the American Negro is probably essentially the same as in the white population. It has occured in American Indians.[56]

It is an uncommon, but by no means rare, disorder. The incidence of the Marfan syndrome is certainly far greater than the general conception of the medical public. The connective tissue defect of the Marfan syndrome is the leading cause of dissecting aneurysm of the aorta in the younger decades. There is reason to believe that there is an appreciable number of very mild cases (*forme fruste*) in whom the connective tissue defect has little or no effect on health or longevity.

Preposterously high estimates of the number of sporadic cases (those derived presumably from *de novo* mutation), as opposed to inherited cases, have been made. My own experience would indicate that no more than 15 per cent of all

cases are new ones. Higher estimates, up to 70 per cent by some writers, are the result of incomplete family studies. How often this mutation occurs in a total population is at present impossible to determine.

The pattern of inheritance is that of a simple Mendelian autosomal dominant (Figs. 7, 8, 9, 11, 12). Parental consanguinity has not been an impressive feature, but exceptions are described.[26] In a few instances, a recessive mode of inheritance seemed to be indicated by the presence of multiple affected members of one sibship with ostensibly normal parents. In only one of the pedigrees of this type which have come to my attention has it been practicable to do thorough investigations of parents and patients (Fig. 9). In the one kinship in which this was possible, I was forced to conclude that the mother was probably affected by a *forme fruste*. This woman had had at least three affected children by one man and one affected child by a second. The occurrence in one male and three females excluded the possibility of a sex-linked recessive trait. There was, therefore, no question but that each of the victims inherited the disease rather than getting it by *de novo* mutation and that the mother carries the gene. On examination, she was found to be 5 feet 8 inches tall, to be moderately long of limb without typical arachnodactyly, and to be myopic but free of ectopia lentis on careful ocular examination. This pedigree demonstrates how it is possible for the student of the full clinical and genetic picture to recognize cases which would be missed otherwise.

To my knowledge there has never been an opportunity to observe the effect of the gene in homozygous state; that is, the union of two affected persons has not been described. Skipping of generations has never been observed in any thoroughly studied pedigree.[68]

Partial submersion of the manifestations of this syndrome, depending apparently on the rest of the genetic milieu in which the mutant gene is operating, has been observed.[92] For instance, when the mutation occurs in unusually pyknic stock, the victim's habitus may be much less impressively unusual. No protection against ocular or aortic abnormality seems to be afforded thereby, however. The fact that in some families pronounced aortic and skeletal abnormalities occur without demonstrable abnormality of the lens structure seems to be further evidence of the operation of the genetic milieu on expression of the syndrome. Differences in the severity of the several components of the syndrome, including absence of some cardinal ones, is not inconsistent with the view that a single mutant gene is primarily responsible for the abnormality.

DIFFERENTIAL DIAGNOSIS

Given stigmata suggestive of the Marfan syndrome, one can be most confident of the diagnosis if ectopia lentis is present in the patient or if other members of the family are unequivocally affected (see Fig. 2). The possibility of the Marfan syndrome is encountered in many situations such as that of aortic regurgitation, otherwise unexplained, in an individual of asthenic and possibly dolichostenomelic habitus. Measurements taken alone are indicative but not completely conclusive. Measurements must be evaluated in the light of a rough

evaluation of the average habitus of the family of which the possibly affected individual is a member. In the first decade of life, comparison of upper and lower segment measurements and of arm span with height is of greater significance because of the relatively short extremities during this period.[154] (For normal values for these measurements during this period see references 40 and 181.) The lack of complete specificity of such measurements is indicated by the occurrence of excessively long extremities on an anthropologic basis in the Denker Negro[102] and on a pathologic basis in the eunuch.[13] The rule of thumb for identification of arachnodactyly—longest digit at least 50 per cent longer than the longest metacarpal—has proved to have both positive and negative error. In the Negro in particular, the Marfan syndrome is often suggested by skeletal proportions. A famous contemporary Negro basketball star is said to be 75½ inches tall, with an arm span of 84-86 inches. Sheldon[144] refers to this habitus as Nilotic dysplasia, since, according to him, inhabitants of the upper Nile area and their descendants display it most often. The Watussi tribe of Uganda is very tall.

A picture mimicking in some respects that of the Marfan syndrome can result from rh incompatibility and from intrauterine rubella infection. Ectopia lentis does not occur in these cases. However, deafness, ocular and cardiac defects, hypotonia, and even arachnodatyly may occur. The presence of some manifestation, such as anophthalmos, which is never encountered in the Marfan syndrome, is a point in favor of one of these other possibilities. Cases simulating Marfan's syndrome have occurred apparently as a result of the occurrence during early pregnancy of febrile illness of unspecified type[54] and of x-ray therapy.[152] (See Fig. 14.)

Institutions for mental defectives often list an unbelievably high percentage of patients with arachnodactyly. This should not be taken to indicate Marfan's syndrome in the majority of instances at any rate, since other evidence indicates that mental retardation is not an integral component of this syndrome and since it is clear that arachnodactyly is a nonspecific manifestation with many possible causes. The patient described by Benda,[17] for example, does not appear to have had a true Marfan syndrome.

Several of the individual components of the Marfan syndrome occur alone or as part of other heritable syndromes and on a genetic basis distinct from the Marfan syndrome. Pectus excavatum,[114,135,147] scoliosis,[55,133] myopia,[37,71] and hernia[44,176] are cases in point. Erdheim's cystic medial necrosis is almost certainly not a homogenesis entity from the etiologic standpoint (see below). Marfan's disease is but one cause, there being other genetic (e.g., Ehlers-Danlos syndrome) and possible acquired causes.

Several genetic varieties of ectopia lentis have been described.[46] One variety of isolated ectopia lentis is inherited as a simple Mendelian recessive.[51,167] I have observed[93] eight children of a first cousin marriage, of whom four had ectopia lentis and four had ateliotic dwarfism (a condition usually inherited as a recessive). Coincidence of the two anomalies occurred in two of the individuals. Another variety of ectopia lentis is inherited as a simple Mendelian dominant as in the Marfan syndrome but as part of the Weill-Marchesani syn-

drome.[92,100,175] The habitus of the victim of the Weill-Marchesani syndrome is diametrically opposite to that of the Marfan syndrome. The victim is brachymorphic, short of stature, with round head, pug nose, depressed nasal bridge, and short, pudgy hands and fingers.

In approximately 70 per cent of instances of congenital ectopia lentis, the anomaly occurs as a component of the Marfan syndrome. The skeletal manifestations of the Marfan syndrome may be so unconvincing in many cases that the presence of ectopia lentis in a patient with cardiovascular signs consistent with the Marfan syndrome should lead one to suspect the diagnosis even though the skeletal changes per se cannot be considered pathognomonic.

Muscular dystrophy was confused for Marfan's syndrome in the patient shown in Fig. 15,*A* and *B*. There were unusually pronounced spinal deformity and long fingers. The patient presented with bacterial endocarditis and aortic regurgitation—additional features suggesting the Marfan syndrome. Autopsy revealed no histologic evidence for this diagnosis but did show changes consistent with a rheumatic basis for the bacterial endocarditis. A brother, subsequently studied (Fig. 15,*C* and *D*) shows unequivocal evidence of muscular dystrophy. In children, the pronounced muscular hypotonia may result in a picture suggesting Oppenheim's amyotonia congenita or Werding-Hoffmann's muscular atrophy.

The relationship, if any, of the Marfan syndrome to "status dysraphicus" is obscure.[117] The latter condition is too ill-defined to make an analysis of relationship possible. We (see Fig. 3,*C*) and others have observed bent fifth fingers, so-called camptodactyly or clinodactyly,[70] and heterochromia iridis,[36] both manifestations which are said to be characteristic of status dysraphicus. Apparently identical clinodactyly is sometimes inherited as an isolated anomaly.[70]

PATHOLOGY

With the exception of the changes in the media of the great vessels and in the heart valves, no specific histologic abnormalities have been detected in this syndrome. In the media of the aorta, the most advanced changes are seen in cases of diffuse dilatation of the ascending aorta in which the process has gone on over several years' time and the patient succumbed to the effects of aortic regurgitation. In such cases, there are frequently early changes in the pulmonary artery. The early changes in the aorta are best demonstrated in those cases dying of dissecting aneurysm.

The advanced changes consist of fragmentation and sparsity of elastic fibers, irregular whorls of seemingly hypertrophied and perhaps hyperplastic smooth muscle, increase in collagenous tissue, pronounced increase in the vascularity of the media with wide dilatation of the vasa vasorum in both the adventitia and the media, cystic spaces occupied by metachromatically staining material. The net result is an aorta which is thicker (but weaker) than normal.

The early changes are those described by Erdheim[41] as cystic medial necrosis.[161] There are mild to moderate degeneration of elastic fiber elements and more or less striking cystic areas filled with metachromatically staining material.

The predominant involvement of the ascending aorta is not inconsistent with a generalized defect of some element of connective tissue, since it is the ascending portion of the aorta which bears the main brunt of hemodynamic stress. Reynolds[129] concluded that, with physiologic pulse pressures, it is only the ascending aorta which shows dilatation (i.e., increase in diameter) with each ventricular ejection. Other observers, while disagreeing with Reynolds' claim that virtually no expansile pulsation occurs beyond the arch, corroborate the finding that much greater expansion occurs in the ascending aorta (15 to 20 per cent increase over diastolic diameter in the ascending aorta, 5 per cent in the distal aorta). Engineers, textile scientists, and others concerned with testing the "strength of materials" are familiar with the fact that cyclical application of a stressing force results in structural disintegration much sooner than does steady application of the same force.

Another factor in the predominant localization in the ascending aorta may be implicit in Laplace's law (wall-tension = pressure × radius). Since both pressure and radius find their largest valves in the ascending aorta, the tension on the wall of that portion is greater than anywhere else in the vascular tree. In the case of aneurysm there is, by the same token, a vicious cycle or self-perpetuating action—the greater the radius, the greater the wall-tension, the greater the radius, and so on.

The predominant localization of the pathologic changes of Marfan's syndrome, of other varieties of Erdheim's cystic medial necrosis (see later), and of syphilis, in the ascending aorta, probably has its basis in the physical and hemodynamic considerations outlined above.

Changes similar to the early ones in the aorta are not uncommon in the main pulmonary artery. Occasionally the changes there are as advanced as are ever seen in the aorta.[166]

Minor changes in the heart valves in the form of marginal thickening or fibromyxomatous excrescenses have been described grossly in many of the autopsied cases,[136,146,162,175] including Salle's[136] case, the first autopsied. Histologically, one case[166] was found to show "numerous lacunas in the collagenous substance of the mitral valve that were filled with a homogeneous basophilic material." This lesion resembles closely that which occurs in the media of the aorta. Fig. 12,*F* represents the changes in the aortic valve in one of our cases. The pronounced sacculation and stretching of the aortic cusps is probably per se evidence of weakness of the connective tissue stroma of the valve. In the process of the stretching, breaks with fenestration of the cusp may occur.[168]

The pathologic studies of the eyes have not been very helpful from the fundamental standpoint. Hypoplasia of the dilator muscle of the iris provides explanation for the miosis and poor response to mydriatics.[79,137]

With the above exceptions (and, of course, the cystic disease of the lung), no histologic abnormalities have been detected. Specifically, peripheral arteries, joint capsules, ligaments, tendons, and periosteum have shown no abnormality, but studies in these areas are distressingly few.

THE BASIC DEFECT

In what element of connective tissue is the defect of the Marfan syndrome located? The histologic appearances in the aorta suggest that the primary defect may be in the elastic fiber. The pathogenic chain of events may be this[68]: The elastic fibers, constitutionally inadequate, undergo degeneration, particularly at the site of maximum hemodynamic stress, the ascending aorta. The smooth muscle elements, which normally have origin and insertion on the elastic lamellae, collapse together into disorganized whorls and undergo hyperplasia and hypertrophy. Reparative processes leave the media scarred. Secondary to the frantic hypertrophy of smooth muscle fibers and the scarring process, dilatation of the vasa vasorum occurs. (In 1933 Wolf[184] suggested that Erdheim's cystic medial necrosis might be a generalized weakness of elastic fibers. He demonstrated abnormalities in larger peripheral arteries and in the main pulmonary artery.)

What the suspensory ligament of the lens has in common with the media of the aorta is obscure. If known, the basic defect of this syndrome might be understood. It is possible to reconcile with a generalized elastic fiber defect many of the other manifestations: the lax joint capsules, the weak ligaments, especially those with large elastic fiber representation such as the ligamenta flava of the spine, the malformed elastic cartilages of the pinnae, and the deformity of the foot where elastic fibers are abundant in the ligaments.[155] But how is one to explain the most striking feature of this syndrome, dolichostenomelia, and the other dolichomorphic features? One gets the impression that the factor that is missing during morphogenesis and growth of bone in victims of this syndrome is a binding force which placed a rein on longitudinal growth. Whether it is elastic fiber as such or some element with the properties of the elastic fiber matters not at the moment. Is some such element missing from the ground material of the cartilaginous precursors of bone? Or is the location of the defect in the periosteum? The periosteum, attached as it is to the epiphyseal cartilage from which longitudinal growth occurs, may exercise control over longitudinal growth. Experiments of Ollier in 1867[109] and of others[80] since him, although not without flaw, suggest such to be the case: If a cuff of periosteum is removed from the circumference of a growing long bone, that bone will grow longer than its untampered counterpart. An inborn weakness of the periosteum might have a similar effect. The bony abnormality does not appear to be one of simple overgrowth since the excess is limited to longitudinal growth. The bones are abnormally small in cross section. Osteogenesis may be proceeding at a normal rate in the periosteum which slides along the diaphysis adding bone to the circumference; the diaphysis may not attain normal transverse dimensions because the periosteal bone is spread over a greater total area.*

*Lacroix[81] writes (p. 59) as follows: "A fibro-elastic membrane, the periosteum grows, while yielding to a traction imposed upon it, by stretching over its entire extent. Where only one zone of growth exists, as in the case of the long bones of the hand and foot, the periosteal sheath is attracted in only one direction; it is pulled in two opposite directions on the two sides of a 'neutral' zone in bones with two zones of growth. Since the diaphysis elongates only at the level of the growth cartilage, the periosteum during development slides along the bone surface at a rate and in a direction specific to each level." Later (p. 67), he writes: "Since the periosteum slides along the diaphysis which it encloses, the youngest trabeculae, those in formation at the moment of examination are not deposited at exactly the same level as those which the same zone of periosteum elaborated in the preceding days." The obliquity of the canals of the nutrient arteries has its origin in this phenomenon.

The precise element of connective tissue which is defective in Marfan's syndrome awaits identification. Nonetheless, it is possible to describe the behavior of the defect in considerable detail.

The production in rats of a somewhat analogous, but *acquired*, syndrome has been of great interest for obvious reasons. Kyphoscoliosis, hernia and aneurysm of the aorta (dissecting, diffuse, or saccular) can be produced in rats (Fig. 16) fed a toxic agent contained in the seed of *Lathyrus odoratus*.[28,120,122] The toxic material has been crystallized[38] and identified[138] as B (γL – glutamyl) aminopropionitrile ($HOOC-\underset{\underset{NH_2}{|}}{CH}-CH_2-CH_2-\overset{\overset{O}{\|}}{C}-NH-CH_2-CH_2-C\equiv N$).

B–aminopropionitrile will also cause skeletal changes and dissecting aneurysm of the aorta.[172] Gelatin and casein appear to afford partial protection against the effects of these toxins.[34] Whether the primary difficulty is in the elastic fibers or in the intermediate material is not clear.[10,32] The demonstration of increased mucopolysaccharide[32] is of interest in light of the metachromatically staining material seen in human cases of Erdheim's cystic medial necrosis including that caused by Marfan's syndrome (see below). Although the basic defect in this acquired syndrome is probably not the same as that in Marfan's syndrome, studies of this sort should be helpful in elucidating some of the many mysteries which surround dissecting aneurysm in particular[79] and disorders of connective tissue in general.

OTHER CONSIDERATIONS

There is, of course, no definitive treatment for this disorder. It should be noted that healing after surgical operations is normal. Herniorrhaphy, orthopedic procedures, and correction of pectus excavatum can be performed with success. (One patient went through a lienorenal shunt procedure for unrelated hepatic cirrhosis.[166]) Correction of pectus excavatum should probably be postponed until after puberty since an imperfect result may follow if there is still opportunity for excessive longitudinal growth of the ribs. The current philosophy in regard to ectopia lentis seems to favor performing lens extraction only if iritis or glaucoma develops. Hufnagel's plastic valve operation[78] was performed in a case of aortic regurgitation on this basis; because of the nature of this disease and of the operation currently practiced, its practicability here is very questionable. Evidence is presented elsewhere[95] that the Hufnagel operation produces widening of the pulse pressure (due both to increase in the systolic level and decrease in the diastolic level) proximal to the valve. This might well increase the strain on the already weakened ascending aorta and accelerate the process of dilatation or predispose further to dissection. In two recent cases (S.L., 293069; S.T., 691351) of idiopathic cystic medial necrosis of the aorta with diffuse dilatation of the ascending aorta and profound regurgitation, Dr. Henry T. Bahnson plicated the dilated aorta and surrounded the ascending aorta as far proximally as possible with a splinting sleeve of synthetic fabric. A happy, although surprising, result of the procedure has been a pro-

nounced decrease in the aortic regurgitation as evidenced by diminution in the diastolic murmur and manifestations of left ventricular strain and by rise in diastolic pressure to almost normal levels. These cases are historic from another standpoint; it is the first time the diagnosis of Erdheim's cystic medial necrosis has been established histologically *in vitam*.

A point of medicolegal importance is the relationship of trauma to the development of various manifestations of the Marfan syndrome. The development of hernia, detachment of the retina,[94,140] dissecting aneurysm,[25,116,149] and total dislocation of the lenses may be intimately related to trauma as an precipitating factor.

In connection with the relation of the Marfan syndrome to other diseases or special physiologic states, rheumatic fever, syphilis, hypertension, and pregnancy might be mentioned. The suggestion of Futcher and Southworth[68] that rheumatic fever may occur with increased incidence in these patients has not been confirmed by further observations. One patient (B.J., J.H.H. 699403) has had severe rheumatic fever and now has unequivocal rheumatic valvular heart disease, but, in general, the incidence is unimpressive. Syphilis and hypertension, if combined with the Marfan disease, might have particularly dire effects on the aorta. There is no careful autopsy documentation of the association, however. There is now convincing evidence of a strikingly increased incidence of dissecting aneurysm of the aorta in pregnancy.[102,141,143] Conceivably, this is related to the hormone "relaxin" and to the general relaxation of ligaments and other joint structures during pregnancy.[1,2,69,115,119,126,187]

Relation to Erdheim's Cystic Medial Necrosis[134].—Erdheim's disease is probably not a single entity from the etiologic standpoint. There are probably a number of possible "causes"—some genetic (like the Marfan syndrome), some acquired in nature. With the control of syphilis and rheumatic fever, cystic medial necrosis will assume increasing importance as a cause of aortic regurgitation. It must be kept in mind particularly when there is no history of syphilis, rheumatism, and bacterial endocarditis and must *not* be excluded from consideration on the grounds that there is no radiologic evidence of aortic dilatation. Unfortunately, the diagnosis of idiopathic Erdheim's disease (Erdheim's disease without the Marfan syndrome) will for the time being need to be a diagnosis of exclusion.

The experience with Marfan's syndrome should prove very useful in the cases of idiopathic Erdheim's disease. In both, dissecting aneurysm or fusiform dilatation* or a combination can occur. In both, the ascending aorta is most severely affected. In both, the process seems to pursue an unrelenting progression to death from rupture of the aorta or from the effects of aortic regurgitation.

There is now convincing evidence[145] that the metabolic turnover rate in the elastic skeleton of the aorta is so low as to raise serious suspicions of complete

*Erdheim's disease is very familiar as a cause of dissecting aneurysm. That it can also cause diffuse or fusiform dilatation of the aorta is indicated by the surgically proved cases referred to above and by reports in the literature.[35,67,131,185,186,187] In some of these, insufficient clinical information is provided to permit exclusion of the Marfan syndrome.

metabolic inertia. The elastic structures of the aorta can be looked on as intended to outlive the rest of the organism. In certain unfortunate individuals, however, the elastica "gives out" prematurely. The result is Erdheim's cystic medial necrosis. Genetic inferiority is probably most frequently the basis. It has been described in brothers,[171] but the clinical information provided is too scant to permit exclusion of the Marfan syndrome. Erdheim's medial necrosis may be the cause of death in the first months of life or not until the ninth decade. Rupture of the aorta possible on a comparable basis is said to occur in horses and occurs in epidemic fashion in turkeys[97] where dietary factors may be responsible.

The treponemal immobilization test for syphilis has created a clinical problem in connection with patients with dilatation of the ascending aorta and aortic regurgitation, who often in the past would have been considered to be syphilitic in spite of negative serologic tests for syphilis of the conventional type. In coming years, cystic medial necrosis of the aorta, previously the exclusive property of the pathologists, will be discussed much more frequently in the clinical literature.

I am indebted to a large number of persons for assistance in accumulating the information presented here. Space does not permit mention of all of them. I would mention specifically Dr. Howard A. Naquin of the Wilmer Ophthalmological Institute. His contemporaneous investigations of ectopia lentis were helpful to the author's study of systemic aspects. Dr. Russell S. Fisher permitted me to examine the file of the Medical Examiner's Office of the City of Baltimore for cases of dissecting aneurysm of the aorta in young persons.

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